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NOVEL APPROACHES TO THE SYNTHESIS OF CARFENTANIL

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Three novel approaches to the synthesis of carfentanil were investigated that did not involve the hydrolysis of the corresponding α-aminonitrile. Starting with commercially available 1-benzyl-4-piperidone, regioselective cleavage of an α,β-exoxysulfone, an aza [3.3] sigmatropic rearrangement and aminolysis of a 1-bromo-1,2-diene were studied. Of these, the most promising was the sigmatropic rearrangement.

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PREFACE

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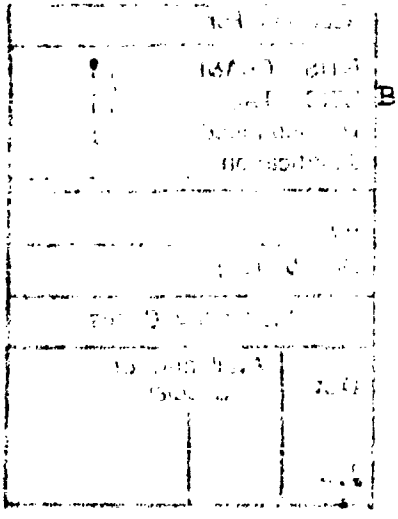

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NOVEL APPROACHES TO THE SYNTHESIS OF CARFENTANIL

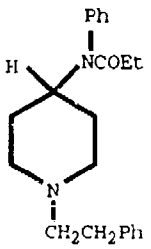
1. INTRODUCTION

Drug action is mediated by means of macromolecular sites which bind to the drug. This idea was suggested in 1905 by Langley, and extensively elaborated by Ehrlich.[1] This binding is often chemo-, regio-, diastereo- and enantiospecific. Binding is not, however, an all-or-nothing phenomenon, and various substances have differing affinity constants for a given receptor. The nature of binding appears to be considerably more complex than the original lock and key paradigm of Emil Fischer, requiring not only complementary geometric features, but also favorable electrostatic forces, hydrogen bonding, hydrophobic interactions, etc.[2] A glove and hand model appears to be closer to the actual binding mechanism, with each participant modifiying its shape to better accommodate the other from the initial interaction to the final binding.

Since the discovery of morphine by Sertürner in 1806, man's knowledge of the mediation of response to intense pain through the administration of opiates (drugs that alleviate intense pain by means of CNS activity)) has grown. Several receptors, μ, δ, and κ, have been identified based on the signal nature of the response to a particular drug as well as antagonism by a specific moiety. The morphine family of analgesics bind to the μ-receptor. Evidence has recently been presented that strongly suggests that there are actually two sites, μ_1 (less selective and μ_2 (morphine-selective.)[2b] {see p.112 for respiratory depression} It has been suggested that κ agonists possessing activity can block the respiratory depressant effects of morphine.[3]

Due to the complexity of response to opiates it was deemed desirable to keep the concentration of the drug low at the receptor. Under these conditions, only the high affinity sites would be affected by the drug. If the analgesic sites are high affinity, then the discovery of extremely potent opiates would be highly desirable. Some success has been realized in the isolation of analgesics from natural products; for example, codeine was extracted by Robiquet in

1832 from morphine's source, the opium poppy (*Papaver somniferum*). The most significant discoveries, however, were made by synthetic chemists, punctuated by the serendipitous discovery of the analgesic properties of meperidine,[4] a readily synthesized compound possessing one-eighth the potency of morphine in man,[5] and the spectacular finding in the 1960's that fentanyl **1** has a potency of almost 300 times that of morphine, . The discovery of fentanyl triggered a flurry of synthetic activity over the next 30 years, using fentanyl as a lead compound. Of the myriad compounds tested, several had very interesting pharmacological profiles.[6] [van Daele, et al.] This report is concerned with a novel synthetic approach to one of these compounds, "carfentanil," N-[1-(2-phenylethyl)-4-methoxycarbonyl-4-piperidinyl]-N-phenylpropanamide **2**.[6,7]



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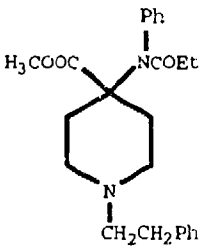

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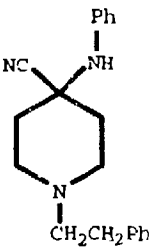


3

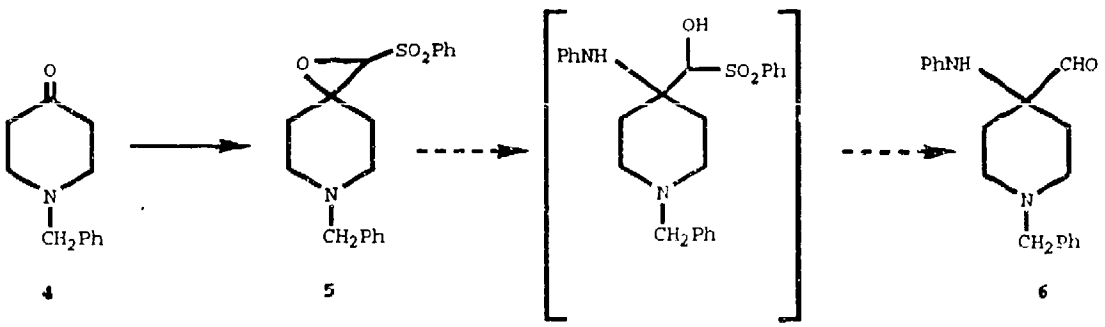
Synthetic approaches to **2** invariably begin with α-aminonitrile **3**, which is readily available from commercially available 1-(2-phenylethyl)-4-piperidone by means of a Strecker synthesis using aniline and potassium cyanide in acetic acid under optimum conditions.[8] Transformation of the 4-cyano function into a methoxymethyl function was fraught with difficulties arising from reversion of **3** to the starting ketone, and the resistance of the intermediate amide to transformation into the ester function by means of the intermediate α-amino acid. Thus, the original Janssen procedure resulted in an overall yield of only 1%.[6] Significant improvements in yield have been achieved in direct transformation of the cyano function into the methoxycarbonyl by Taber.[9] Conversion of the carboxamide into the methoxycarbonyl group in a slightly different system has been successfully effected.[10] Feldman and Brackeen[11] developed a synthesis that depended on the transformation of **3** to an hydantoin, an intermediate in a classical route to α-amino acids.[12]

We sought to develop novel synthetic routes for **2** that would not proceed through **3**. The starting material in this investigation was commercially available 1-benzyl-4-piperidone. The protecting benzyl function can be readily cleaved by means of catalytic hydrogenation, and the resulting piperidine alkylated with 1-chloro-2-phenylethane to provide **2**.

2. RESULTS AND DISCUSSION

Our first approach to **2** is outlined in Scheme 1.

Scheme 1

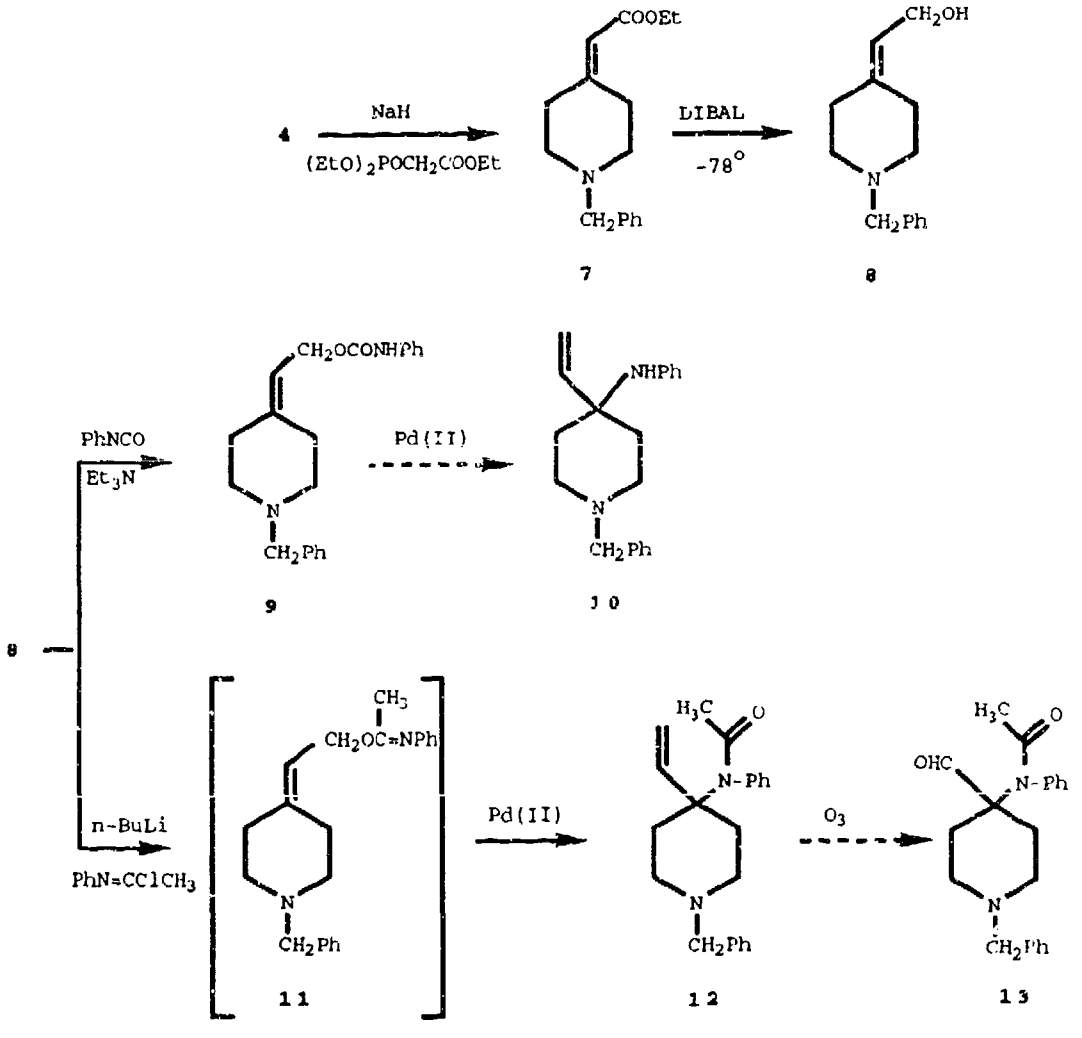


Incentive for pursuing this route was supplied by the finding that α-azido aldehydes can be obtained by azide ion ring cleavage of α,β-epoxysulfones. This reaction has been exploited in the synthesis of α-amino acids and branched sugars.[13] Opening of α,β-epoxysulfone **4** with aniline is the key reaction in this sequence. This reaction should occur regioselectively, yielding in principle a-anilinoaldehyde **5** which, after oxidation, would a-amino acid **6**. Darzen reaction of 1-benzyl-4-piperidone with chloromethylphenylsulfone.[14] led to isolation of **5** in 97% yield. Aminolysis of oxiranes has been found to occur readily in the presence of Lewis acids[15,17] or metal ions.[18] Accordingly, **4** was treated with alumina, a Lewis acid, using Posner's method.[19] Under these conditions, the starting material decomposed. Similar results were obtained with cobalt (II) chloride[20], titanium isopropoxide[16] and lithium

perchlorate.[18] Even the Grignard reagent, anilinomagnesium bromide, failed to give the desired product.

The second approach to **2** was based on an aza [3.3] sigmatropic rearrangement of unsaturated urethane **7**. Thermal

Scheme 2



and metal-catalyzed rearrangements of allyl imidates have

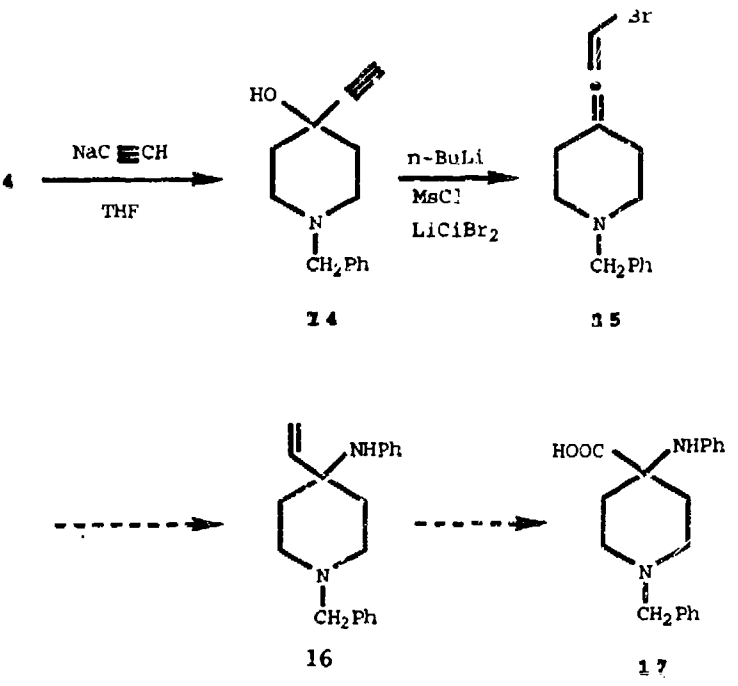
provided a convenient means of formation of allylic carbon-nitrogen bonds.[21,22] The required carbamate **5** was prepared from **4** by means of a Horner-Emmons modification of the Wittig reaction. The ethoxycarbonyl function of **7** could be carefully reduced with diisobutylaluminum hydride (DIBAL) at -78°. Treatment of **8** with phenylisocyante in triethylamine gave **9** in an overall yield of 65%.

Attempted [3.3]sigmatropic rearrangement of **9** with a catalytic amount of $Pd(PhCN)_2Cl_2$ in refluxing toluene or xylene led to recovery of starting material.

Failure to achieve [3.3] sigmatropic rearrangement with carbamate **9** prompted consideration of imidate **11** which has preexisting C=C and C=N bonds. Accordingly, **8** was treated with n-BuLi, followed by phenylacetamide. The crude product was treated directly with $Pd(PhCN)_2Cl_2$ and refluxed in toluene for 15 h. Flash chromatography of the crude product produced **12** in 20% yield. A preliminary study of the ozonolysis of **10** did not result in formation of desired anilidoaldehyde **13**, but rather polar material that proved difficult to isolate and characterize. It is possible that ozonolysis was nonchemoselective, occuring not only at the desired position, but also at the ring nitrogen as well.

A third approach was suggested by the work of Caporusso and coworkers[25] who found that propargylamines were obtained in high yield by aminolysis of 1-bromo-1,2-dienes[24] in the presence of copper(I) bromide. For example, under these conditions, cyclohexylallene gave 1-ethynyl-1-aminocyclohexane. Thus, a preparation of bromoallene **15** was sought. The route for conversion to desired amino acid **17** is presented in Scheme 3. Bromoallenes have been prepared from α-ethynyl alcohols.[25,26] When **4** was treated with sodium acetylide, an 80% yield of alcohol **14** was isolated. When **14** was subjected to the reported procedures[27,28] no **15** was obtained. It is likely that $LiCuBr_2$ formed a complex with the ring nitrogen rather than participating in mesylate displacement.

Scheme 3



3. EXPERIMENTAL METHODS

^{1}H and ^{13}C NMR spectra were recorded with a Varian XL-300 spectrometer operating at 300.0 and 75 MHz respectively. Chemical shifts are reported in δ values using tetramethylsilane as in internal standard. Chemical ionization mass spectrometry was done with 10% NH_3 in methane with a source temperature of 150°. Tetrahydrofuran (THF) was distilled from benzophenone ketyl under an argon atmosphere.

3.1 **2'-Phenylsulfonyl-5-benzyl-1-oxa-5-azaspiro[2.5]octane (5).** To a solution of chloromethylphenyl sulfone (5.03 g, 26.4 mmol) and 1-benzyl-4-piperidone (5.00 g, 26.4 mmol) in 100 mL of dry THF maintained at -10° was added a solution of potassium tert-butoxide (2.96 g, 26.4 mmol) in tert-butanol. The reaction mixture was then allowed to come to room temperature and was stirred for 8 h. It was then poured into 500 mL of water and extracted with ether. The ether extracts

were combined, dried (Na_2SO_4) and concentrated, providing a viscous brown material. The crude product after purification by flash chromatography on silica gel using 1:1 ethyl acetate/petroleum ether (v:v) provided 8.8.g (97.0%) of **5**, mp = 80 - 82° C. ^{1}H NMR 1.45 - 1.55 (m, 1H); 1.85 - 1.95 (m, 1H); 2.35 - 2.85 (m, 6H); 3.55 (d, 2H, C***H***$_2$Ph); 3.80 (s, 1H); 7.20 - 7.40 (m, 5H, aromatic protons); 7.55 - 7.70 (m, 3H, aromatic protons); 7.95 (d, 2H, aromatic protons). ^{13}C NMR: 32, 48, 49, 56, 62, 114, 114.5, 117, 120, 125, 126, 128, 128.7, 128.9, 129, 138, 145, 170. Anal. Calcd for $C_{19}H_{21}NSO_3$: C, 66.5; H, 6.1; N, 4.1. Found: C, 66.5; H, 6.1; N, 4.1.

3.2 **1-Benzyl-4-[(ethoxylcarbonyl)methylene]piperidine (7).** Sodium hydride (2.21 g of a 60% suspension in mineral oil, 55.2 mmol) was washed twice with 50 mL of pentane under a nitrogen atmosphere and then 50 mL of dry THF was added. Triethylphosphonoacetate (12.35 g , 55.10 mmol) was added dropwise 30 min before the addition of **4** (10.43 g , 55.50 mmol). The mixture became yellow and sticky. After 20 min the reaction mixture was agitated with 500 mL of water and extracted with Et_2O. The ether layers were dried (Na_2SO_4) and concentrated to yield a quantitative yield of the ester, ^{1}H NMR: 1.25 (t, 3H, C***H***$_3$); 2.3 - 3.0 (m, 6H); 3.5 (s, 2H, C***H***$_2$Ph); 4.12 (q, 2H, C***H***$_2$); 5.62 (s, 1H, C***H***); 7.35 (s, 5H, aromatic).

3.3 **1-Benzyl-4-[(1-hydroxymethyl)methylene)]piperidine (8).** Diisobutylaluminium hydride (100 mL, 1.0 M in THF, 100 mmol) was added dropwise to a solution of **7** (14.5 g, 55.9 mmol) in CH_2Cl_2 at -78° C. The reaction mixture was stirred for an additional 2 h, brought to 0° C, and quenched with saturated aqueous NH_4Cl, followed by addition of 40 mL of 1N NaOH. The mixture was filtered through a Celite pad. The organic layer was separated, and the aqueous layer extracted with ether. The combined organic layers were dried (Na_2SO_4) and concentrated. Purification by silica gel chromatography, eluting with 2:1 ethyl acetate/petroleum ether (v:v), provided 10.7 g (87.0%) of product, ^{1}H NMR: 2.20 - 2.50 (m, 8H); 3.5 (s, 2H, C***H***$_2$Ph); 4.15 (d, 2H, C***H***$_2$OH); 5.40 (t, 1H, C***H***); 7.20 - 7.25 (m, 5H, aromatic).

3.4 **N-[(1-Benzyl-4-piperidilenyl)methoxycarbonyl]aniline (9).** To a solution of allyic alcohol **8** (1.5g, 6.9 mmol) in 40 mL of dry CH_2Cl_2 was added 1.9 mL (13.6 mmol) of triethylamine, followed by addition of 1.2 mL (10 mmol) of phenylisosyanate. The reaction mixture was stirred overnight at room temperature. Saturated aqueous NH_4Cl (30 mL) was added, and after the organic layer was separated, the aqueous

layer was extracted with CH_2Cl_2 . After drying Na_2SO_4), the combined organic layers were concentrated and passed through a silica gel column, eluting with 1:1 ethyl acetate/petroleum ether (v:v), to yield 2.14 g (92.1%) of carbamate **8**. mp = 80 - 82° C. ^{1}H NMR: 2.2 - 2.5 (m, 8H); 3.5 (s, 2H, C***H***$_2$Ph); 4.6 (d, 2H, C***H***$_2$ OCONHPh); 5.4 (t, 1H, C***H***); 6.65 (br. s, 1H, N***H***); 7.0 - 7.5 (m, 10H, aromatic). Mass spec: 337 (M^+), 293, 200. Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.9; H,7.0; N, 8.3. Found: C, 74.3; H, 7.1; N,8.3.

3.5 **1-Benzyl-4-ethylnyl-4-piperidinol (14).** Sodium acetylide (15 mL, 18% suspension in xylene) was added to a solution of 5.00 g (26.4) of **4** in 40 mL of THF. The reaction mixture was stirred at 40 - 50° C for 6 h. After cooling the reaction mixture was mixed with an equal volume of water, and the aqueous phase dried over $MgSO_4$. Concentration gave a yellow solid that was collected by filtration, and washed several times with n-pentane to provide 4.5 g (80%) of **14**, mp = 152 - 153° C. ^{1}H NMR: 1.9 - 2.8 (m, 10H): 3.5 (s, 2H, C***H***$_2$Ph); 7.2 - 7.4 (m, 5H, aromatic). Mass spec: 215 (M^+), 189.

3.6 **N-(1-Benzyl-4-vinyl-4-piperidinyl)-N-phenylethanamide (12).** A mixture of PCl_5 (7.25 g, 35.0 mmol) and N-phenylacetamide (4.72, 35.0 mmol) in benzene (25 mL) was refluxed for 1 h. After removal of the solvent and $POCl_3$ in vacuo, the reaction vessel was filled with Ar, and 10 mL of dry THF was added. This solution was added dropwise to the lithium alkoxide solution prepared by the dropwise addition of 2M n-BuLi (18.9 mL, 38,8 mmol) to 8.44 g (38.8 mmol) of allylic alcohol **8** at 0° C, followed by stirring for 30 min. The resulting mixture was stirred at room temperature for 15 h. The solvent was removed and the residue dissolved in CH_2Cl_2. After washing with saturated aqueous NH_4Cl, the organic layer was dried (Na_2SO_4) and concentrated to give the crude imidate **11**. ^{1}H NMR: 1.4 (t, 3H, C***H***$_3$); 2.2 - 2.4 (m, 8H); 3.75 (s, 2H, C***H***$_2$Ph); 4.8 (d, 2H, C***H***$_2$); 5.5 (s, 1H, C***H***); 7.0 - 7.8 (m, 10H, aromatic).

The crude imidate was dissolved in dry toluene and $Pd(C_6H_5CN)_2Cl_2$ (500 mg) was added. The reaction mixture was refluxed overnight, and after cooling and removal of solvent, the product was isolated by chromatography on silica gel, eluting with 1:1 ethyl acetate/petroleum ether (v:v) in 20% yield (2.04 g). ^{1}H NMR: 1.4 - 2.7 (m, 8H); 3.5 (s, 2H, C***H***$_2$Ph); 5.2 (q, 2H, C***H***$_2$); 6.0 (m, 1H, C***H***); 6.7 (s, 1H, N***H***); 6.6 - 7.2 (m, 10H, aromatic). Mass spec: 292 (M^+), 200.

4. CONCLUSIONS

Three novel synthetic approaches to the extremely potent opioid, carfentanil, have been explored. These were cleavage of a phenylsulfonyl epoxide by aniline, an aza [3.3] sigmatropic rearrangement, and aminolysis of a bromoallene. While time did not permit a rigorous exploration of any of these routes, the chemistry reported here should serve as a point of departure for additional research on synthetic routes that are not based on α-aminonitrile hydrolytic routes.

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